Sertoli–Leydig cell tumour in an infertile patient after stimulated ovulation

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A 36 year-old infertile female developed a stage IV (FIGO) ovarian carcinoma consisting of a poorly differentiated Sertoli–Leydig cell tumour after receiving one course of ovulation induction with follicle stimulating hormone (FSH), human menopausal gonadotrophin (HMG) and human chorionic gonadotrophin (HCG) followed by gonadotrophin-releasing hormone analogue (GnRHa). The patient died of liver metastasis and hepatic failure 41 months after first diagnosis, despite aggressive treatment consisting of debulking surgery and aggressive adjuvant chemotherapy.

Key words: ART/infertility/Sertoli–Leydig cell tumour/stimulated ovulation

Introduction

Ovarian stimulation is the preliminary procedure of all assisted reproductive techniques (ART) in infertility treatment. Several articles have reported the presence of ovarian cancers in infertile females receiving clomiphene citrate and gonadotrophin. There has been much debate on the ‘incessant-ovulation and ovarian cancer of epithelial origin’ hypothesis. Nevertheless, the relationship between ovarian cancer and stimulated ovulation still remains uncertain. In literature reports concerning association between ovarian carcinomas and stimulated ovulation, serous adenocarcinoma has been the second most common histological type (Atlas et al., 1982; Carter et al., 1987; Kulkami et al., 1989; Dietl, 1991; Goldberg et al., 1992; Lopes et al., 1992; Balasch et al., 1993). Willemsen (1993) described 12 granulosa-cell tumours, this being the second most common type. Other investigators have presented cases of mucous cystadenoma (Grimbizis et al., 1995) and endometroid ovarian carcinoma (Bamford et al., 1982). To our knowledge, this is the first report of a Sertoli–Leydig cell tumour in an infertile female receiving ART.

Case report

A 36 year old female entered our protocol of ART following the diagnosis of primary infertility for 15 years. Due to anovulation and asthenozoospermia (motility 27.8%) and consideration of her age, she received one cycle of ovulation induction with follicle stimulating hormone (FSH; Metrodin, Serono Laboratories, Rome, Italy), human menopausal gonadotrophin (HMG; Pergonal, Serono) and gonadotrophin-releasing hormone analogue (GnRHa; leuprolide acetate, LA, Lupron, Abbott Medical, Chicago, USA) (long protocol, Shan, Tao-Yuan, Taiwan 10591, Republic of China or Ayes, Rome, Italy), human menopausal gonadotrophin (HMG; Pergonal, Serono) and gonadotrophin-releasing hormone analogue (GnRHa; leuprolide acetate, LA, Lupron, Abbott Australasia PTY Ltd., Kurnell, NSW, Australia) (long protocol, 1 mg/day × 10 days in the mid-luteal phase). Two oocytes were retrieved from the left ovary and inseminated in vitro. Unfortunately, the oocytes did not show two pronuclei 24 h after insemination. Intracytoplasmic sperm injection (ISCI) was performed to re-inseminate the unfertilized oocytes, but in vain. During the course of stimulated ovulation, an ovarian cyst, 3.2×2.5 cm, was observed in the right ovary. During oocyte retrieval, a chocolate-like fluid was drained from the right ovarian cyst, which confirmed the diagnosis of endometrioma. Danazol 800 mg was administered daily to treat the endometriosis for 1 month. The regimen was changed to leuplin depot 3.75 mg s.c. injection once a month in the following 2 months. Ten days after the second dose of leuplin depot, she was admitted with pleomorphic and anaplastic nuclei. Immunochemical study showed that the Sertoli tubular cells were positive for vimentin only. These findings established the diagnosis of Sertoli–Leydig cell tumour of intermediate grade. Despite two courses of chemotherapy with cisplatin (100 mg/m2), etoposide (100 mg/m2, D2,3,4) and bleomycin (25 mg/m2, D2,3,4), the patient died of hepatic failure.
Figure 1. The tumour is mainly composed of Sertoli cell tubules with rare Leydig cell clusters.

Discussion
Fathalla (1967) and Stevenson (1970) first reported that patients with endometriosis had a higher incidence of ovarian cancer. Despite extensive study of ovarian cancers, no definite aetiology has been established. However, several risk factors and protecting factors for ovarian cancer have been found in previous research. Patients with infertility have a higher incidence of epithelial ovarian cancer (Lingeman, 1983; Negri et al., 1991). In contrast, pregnancy and the use of oral contraceptives are thought to have protective roles (Heintz et al., 1985; Wu et al., 1988). Fathalla (1971) proposed the hypothesis that ovarian cancer was related to incessant ovulation. Zajicek (1977) also observed the association between ovarian cystomas and ovulation. This supported the possibility of the malignant transformation of ovarian surface epithelium and follicle lining epithelium during repeated trauma and repairing. Meanwhile, oral contraceptive pills and pregnancy can protect the ovary by suppression of ovulation (Scott, 1984).

Whittemore et al. (1992) reported that infertile females using fertility drugs were 27 times more likely to develop ovarian cancer than a fertile female. These results were reappraised by Balasch et al. (1993), who disputed the relationship between ovarian cancer and fertility treatment. The cause of increased risk of ovarian cancer in infertile patients may be the underlying disorder, rather than the use of fertility drugs. In the current case, the long protocol of GnRHa plus FSH (metrodin, 150 IU×8 days), HMG (Pergonal, two ampoules×9 days) followed by HCG (10 000 IU) was used for one cycle. Before initiating ovulation induction, a small cyst diagnosed as endometrioma was noted and persisted through stimulated ovulation to oocyte retrieval. During oocyte retrieval, transvaginal sonographic examination demonstrated an endometrioma in the right ovary, the diagnosis being proved by the chocolate-like content. No abnormal mass implying ovarian tumour or Sertoli–Leydig cell tumour was found in the same scan. The relationship between fertility drugs and Sertoli–Leydig cell tumour was not definite.

Leuplin depot is a type of GnRHs which reduces the release of luteinizing hormone (LH) and FSH by down-regulation. Immediately after administration of GnRHa, a period of up-regulation occurs which usually lasts 4–6 days. Feldberg et al. (1989) reported ovarian cyst formation in five of the 22 patients in the period of up-regulation after buserelin (900 mg, days 1–3; Superfact, Hoechst A.G., Frankfurt, Germany) administration. Whether or not the repeated up-regulation of GnRHa is one of the factors inducing the malignant transformation of a silent tumour remains uncertain.

Reviewing the case reports, ovarian cancers associated with infertility were predominantly serous adenocarcinoma or granulosa cell carcinoma. To our knowledge, no case of Sertoli–Leydig cell tumour has been reported similar to the current one. Sertoli–Leydig cell tumours are usually divided into three groups based on the differentiation: good, intermediate and poor. The survival rate is significantly higher in patients in the good differentiation category, as compared to patients in the moderate and poor differentiation categories (Scully, 1979; Roth et al., 1981; Zaloudek et al., 1984; Young et al., 1985). The current case was a poorly differentiated stage IV disease. The interval between diagnosis to mortality was $4\frac{1}{2}$ months despite aggressive adjuvant chemotherapy following debulking surgery.

Although no direct connection can be found between fertility drugs and ovarian cancer, a tumour of rapid growth is noteworthy. It should be kept in mind that ascites occurring in patients receiving ovulation induction may indicate a diagnosis of ovarian cancer other than ovarian hyperstimulation syndrome. Patients with endometrioma should be closely followed up with CA-125 measurement and sonography performed through the course of ovulation induction and even after oocyte retrieval. Moreover, cells retrieved during oocyte retrieval should be subjected to cytological examination to rule out the possibility of malignant change.
References

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